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Risk stratification of elderly patients with acute pulmonary embolism

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Nomenclature and Abbreviations

AUC	Area under the ROC curve
DVT	Deep vein thrombosis
hs-CRP	High-sensitivity C-reactive protein
hs-cTnT	High-sensitivity cardiac Troponin T
IDI	Integrated discrimination improvement
NRI	Net reclassification improvement
NT-proBNP	NT-pro B-type natriuretic peptide
PE	Pulmonary embolism
PESI	Pulmonary embolism severity index
ROC	Receiver operating characteristic
SWITCO65+	SWIss venous Thromboembolism COhort of patients aged ≥65 years
VTE	Venous thromboembolism

Essentials

- Do hs-cTnT, NT-proBNP, hs-CRP improve risk prediction of patients with pulmonary embolism (PE) beyond the PESI risk score?
- In elderly patients with PE we studied the PESI risk score and these 3 markers for 6-month mortality.
- Adding these markers to the PESI risk score had no clinically relevant impact on risk stratification.
- In elderly patients with PE, 6-month mortality can be predicted by the PESI risk score alone.

Abstract

Background: Combining high-sensitivity cardiac Troponin T (hs-cTnT), NT-pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP) may improve risk stratification of patients with pulmonary embolism (PE) beyond the PESI risk score.

Methods: In the prospective multicenter SWITCO65+ study, we analyzed 214 patients ≥65 years with a new submassive PE. Biomarkers and clinical information for the PESI risk score were ascertained within 1 day after diagnosis. Associations of hs-TnT, NT-proBNP, hs-CRP and the PESI risk score with the primary endpoint defined as 6-month mortality were assessed. The discriminative power of the PESI risk score and its combination with hs-cTnT, NT-proBNP and hs-CRP for 6-month mortality was compared using integrated discrimination improvement (IDI) index and net reclassification improvement (NRI).

Results: Compared with the lowest quartile, patients in the highest quartile had a higher risk of death during the first 6 months for hs-cTnT (adjusted HR 10.22; 95% CI 1.79-58.34; p=0.009), and a trend for NT-proBNP (adjusted HR 4.3; 95% CI 0.9-20.41; p=0.067) unlike hs-CRP (adjusted HR 1.97; 95% CI 0.48-8.05; p=0.344). The PESI risk score (c-statistic 0.77 (95% CI 0.69-0.84) had the highest prognostic accuracy for 6-month mortality, outperforming hs-cTnT, NT-proBNP and hs-CRP (c-statistics of 0.72, 0.72, and 0.54), respectively. Combining all three biomarkers had no clinically relevant impact on risk stratification when added to the PESI risk score (IDI = 0.067; 95% CI 0.012-0.123; p=0.018; NRI = 0.101 95% CI -0.099-0.302; p=0.321).

Conclusions: In elderly patients with PE, 6-month mortality can adequately be predicted by the PESI risk score alone.

Introduction

Venous thromboembolism (VTE) is a major contributor to global morbidity and mortality [1]. The incidence of VTE increases with higher age and hospital-associated VTE is an important cause of disability-adjusted-life-years lost, especially in low- and middle-income countries [1, 2].

Within the spectrum of VTE, pulmonary embolism (PE) constitutes a potentially life-threatening condition: The short-term mortality of PE ranges from less than 2% in low-risk patients to more than 95% in patients with cardiac arrest following PE [3-5]. In patients with PE without hemodynamic instability, the individual risk of early mortality can be estimated by determination of the Pulmonary Embolism Severity Index (PESI) risk score [6, 7] as recommended by the current European Society of Cardiology (ESC) guidelines to identify very low-risk patients eligible for outpatient treatment [8]. While the PESI risk score is exclusively based on clinical parameters, recent data have shown that the addition of cardiovascular biomarkers, such as high-sensitivity cardiac troponin T (hs-cTnT) and the precursor of brain natriuretic peptide, N-terminal pro-brain natriuretic peptide (NT-proBNP) may further improve risk stratification for PE-related complications or PE-related mortality in elderly hemodynamically stable patients with PE [8-10]. Of note, these previous studies did not specifically relate the added value of these markers to the PESI risk score for all-cause mortality and C-reactive protein was not included. Indeed, at 3 months, all-cause mortality is more frequent than PE-related mortality (6.5% vs. 2.3%) [11].

Systemic inflammation is a central component of cardiovascular risk with the circulating C-reactive protein (CRP) representing the most extensively studied pro-inflammatory biomarker. In particular, high-sensitivity CRP (hs-CRP) was found to be accurate in cardiovascular risk prediction in primary [12] and secondary prevention after acute coronary syndromes [13] where it guided an anti-interleukin 1β antibody therapy to reduce major adverse cardiovascular events [14].

Unlike in coronary and other atherosclerotic diseases [15-18], the role of hs-CRP in VTE remains less clear: Controversy remains on its role in risk stratification *before* the occurrence of VTE [19-21], whereas levels of hs-CRP were consistently found to be elevated *after* a VTE episode [22, 23]. A small study related hs-CRP levels to short-term in-hospital outcome: The authors found increased hs-CRP levels in patients with decreased reperfusion after fibrinolytic therapy and in patients with massive PE [24]. However, the role of hs-CRP in risk stratification after pulmonary embolism (PE) *without* hemodynamic compromise in elderly patients remains unclear.

Thus, we compared the prognostic accuracy of hs-CRP with cardiac biomarkers (hs-cTnT, NT-proBNP) and investigated whether these biomarkers provide incremental prognostic value to predict all-cause mortality beyond the PESI risk score in elderly patients with acute PE without hemodynamic instability.

Materials and Methods

Patient population

Consecutive patients with a diagnosis of VTE aged ≥65 years were enrolled into the SWIss venous Thromboembolism COhort (SWITCO65+) study between September 2009 and March 2012 (ClinicalTrials.gov; NCT00973596).

The SWITCO65+ study is a prospective multicenter cohort study on long-term medical outcomes in patients aged ≥65 years with acute, symptomatic deep vein thrombosis (DVT) or PE from five university hospitals and four high-volume non-university hospitals in Switzerland [25]. Only patients with an objectively diagnosed acute symptomatic, haemodynamically stable PE, in whom blood samples were drawn within 24 hours after the diagnosis of PE and clinical information to calculate the PESI risk score was ascertained within the first day after diagnosis were analysed in the current study. Symptomatic PE was defined by a positive test using spiral computed tomography or pulmonary angiography or a high probability ventilation-perfusion scan in patients with acute chest pain, new or worsening dyspnoea, haemoptysis, or syncope [25].

Exclusion criteria comprised catheter-related thrombosis, thrombosis at different site than lower limb, insufficient ability to understand German- or French, inability to provide informed consent, conditions incompatible with follow-up (e.g., terminal illness), and previous enrolment in the same study. In the current analysis patients had to be treated with anticoagulation and had to be free of severe infection or sepsis in the preceding 3 months. The study was approved by the local ethics committees. Informed consent was obtained from all study participants. A detailed description of the study methods has previously been published [25].

Clinical and laboratory characteristics

Baseline demographic and clinical data (age, gender, body mass index (BMI), systolic blood pressure, heart rate, respiratory rate, arterial oxygen saturation, smoking status) as well as data on medication (lipid lowering medication, estrogen therapy, antiplatelet medication; initial vitamin K antagonists (VKA) and initial parenteral anticoagulation) were collected by trained study nurses and recorded on standardised data collection forms. Clinically relevant comorbidities (diabetes mellitus, arterial hypertension, coronary artery disease, chronic/acute heart failure, chronic lung disease, chronic liver disease, chronic renal disease, active cancer, severe infection or sepsis, and history of major bleeding) were documented. The history of prior VTE was also routinely obtained in all patients. The presence of an underlying cause of VTE was determined to differentiate between provoked vs. unprovoked VTE.

The PESI risk score was determined in all included patients based on available clinical data ascertained at study inclusion within 24 hours. Routine blood work was performed locally, comprising leukocyte, platelet, haemoglobin, and D-dimer concentrations, respectively. All data were entered in an electronic database.

Biomarker measurements

Venous blood was drawn at the time of enrolment and centrifuged at 2700g for 10 min at room temperature to obtain serum, frozen, and stored in aliquots at -80°C at University Hospital Lausanne (central biobank) until serial measurement (no prior freeze-thaw cycles). In the current study, only patients with blood drawn within 1 day of diagnosis of PE were analysed. NT-proBNP and hs-cTnT were measured in serum aliquots at University Hospital Geneva using an electrochemiluminescence immunoassay (cobas e602 reader; Roche Diagnostics, Mannheim, Germany) and hs-CRP was measured at University Hospital Zurich in serum aliquots using a latex-enhanced immunoturbidimetric assay on a cobas c501 autoanalyser (Roche Diagnostics, Mannheim, Germany) with assay characteristics as reported by the manufacturer.

Clinical endpoints

A clinical follow-up visit was performed at 3 months and a telephone follow-up at 6 months. The primary outcome for this study was all-cause mortality within 6 months after diagnosis of PE enabling assessment of the prognostic accuracy of biomarkers against the PESI risk score as a reference model [6, 7].

Outcomes were assessed using patient or proxy interviews, interview of the patient's primary care physician, and/or hospital chart review. A committee of three blinded, independent clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to PE, possibly due to PE, due to major bleeding, or due to another cause. Final classifications were made on the basis of the full consensus of this committee [25].

Statistical analyses

Hs-CRP, hs-cTnT, and NT-proBNP levels were categorised into low, medium, and high level groups using the 25th and 75th percentile as pre-specified cut-offs.

We examined associations between log-transformed and categorized biomarker values and the time to all-cause death up to six months using ordinary Cox regression with robust standard errors. We used competing risk regression according to Fine and Gray [26] to explore the association between biomarker values and the time to PE- and cancer-related death and the time of a first VTE recurrence and a first major bleeding up to six months, accounting for non-PE-, non-cancer-, and non-bleeding-related death as a competing event, respectively. The strength of the association between biomarker levels and the event is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of a competing risk. Models were adjusted for clinical variables previously shown to be associated with the respective outcome and periods of anticoagulation as a time-varying covariate. All-cause mortality was adjusted for age, gender, active cancer, provoked VTE, heart failure, chronic lung disease, and periods of anticoagulation as a time-varying covariate. We assumed missing values in adjustment variables to be normal/absent.

The discriminative power of the PESI risk score, hs-CRP, hs-cTnT, NT-proBNP, and combinations thereof, for 6-month mortality was assessed by Harrell's C concordance statistic for time-to-event outcomes and the area under the ROC curve (AUC) for binary outcomes. The added predictive ability of single biomarkers and combinations of biomarkers when added to the PESI risk score were assessed by the integrated discrimination improvement (IDI) index and the net reclassification improvement (NRI). The IDI is based on a logistic model and was calculated by the method of Pencina et al. [27]. Different linear combinations of biomarkers and the PESI risk score were derived from predictions of logistic models with 6-month mortality as dependent and the relevant biomarkers and the PESI risk score as independent variables. In addition, we performed sensitivity analyses for all patients in whom a biomarker measurement was available irrespective of timing of blood draw as well as for patients without

cancer. P-values <0.05 were considered statistically significant. All analyses were performed using Stata 14 (Stata Corporation, College Station, Texas, U.S.A.). Reporting of the study conforms to STROBE statement along with references to STROBE statement and the broader EQUATOR guidelines [28, 29].

Results

Prospective SWITCO65+ PE cohort – clinical and laboratory characteristics

Of 695 patients with PE enrolled in SWITCO65+, 214 patients were included in the current analysis (**Figure 1**). Median age in this cohort was 75.0 years (IQR 69.0; 82.0) and one third of patients had had a prior VTE (n=67, 31%) or a provoked PE (n=64, 30%) and 15% (n=32) of patients had active cancer. Clinical characteristics of analysed patients, including their biomarker levels, are shown in **Table 1** – comprising an intermediate risk cohort of patients (median PESI risk score of 94.0). Distribution of biomarker levels across PESI risk score classes are shown in **Supplemental Table S1**. In order to address a potential selection bias of the patients included vs. excluded patients, we performed a comparison of baseline characteristics between included and excluded patients (**Supplemental Table S2**). These two patient groups were very similar regarding baseline characteristics except for differences in blood counts attributable to exclusion of patients with infection or sepsis. Nonetheless, 6-month mortality was higher in in- vs. excluded patients, possibly attributable to a higher burden of inflammation (hs-CRP) and higher ventricular strain (NT-proBNP).

Discrimination of risk by hs-cTnT, NT-proBNP and hs-CRP for all-cause mortality

During the first 6 months of follow-up, 29 patients (13.6%) died due to various reasons; 10 of whom died due to PE, 8 died from cancer (**Supplemental Table S3**). Patients in the highest quartile had a significantly higher risk to die during the first 6 months for hs-cTnT (adjusted HR 10.22; 95% CI 1.79-58.34; p=0.009) with a trend for NT-proBNP (adjusted HR 4.3; 95% CI 0.9-20.41; p=0.067) compared with the lowest quartile. Conversely no significant difference was found for hs-CRP when comparing the highest quartile with the lowest quartile (adjusted

HR 1.97; 95% CI 0.48-8.05; p=0.344) (**Supplemental Table 4)**. Associations of individual biomarkers with all-cause mortality during 6-month follow-up are shown in **Table 2**.

Prognostic accuracy of hs-CRP, hs-cTnT and NT-proBNP for all-cause mortality, alone and combined with PESI risk score

Among the three biomarkers and the PESI risk score, the prognostic accuracy of hs-CRP (c-statistic 0.54, CI 0.44-0.64) to predict mortality at 6 months was poor (**Table 2, Figure 2**). In contrast, hs-cTnT (c-statistic 0.72, CI 0.62-0.81), NT-proBNP (c-statistic 0.72, CI 0.63-0.80) and the PESI risk score (c-statistic 0.77, CI 0.69-0.84) showed good discrimination for 6-month mortality.

Combining all three biomarkers with the reference model (PESI risk score) provided incremental discrimination of risk for all-cause mortality as assessed by IDI but not by NRI (**Table 3**).

We additionally evaluated the predictive ability for 30-day mortality. Results are similar as for 6-month mortality (**Supplemental Tables S5-S6** and **Figure S1**).

To address whether results were similar for patients in whom a biomarker measurement was available irrespective of timing of blood draw (n=551), a sensitivity analysis was performed. The PESI risk score remained the best discriminator of risk and was only marginally improved by the addition of the three biomarkers (c-statistic 0.77 to 0.80) (**Supplemental Tables S7-S9**).

A subgroup analysis excluding cancer patients showed similar results with good prognostic accuracy for 6-month mortality for the PESI risk score with a slightly higher increment in discrimination of risk when adding hs-cTnT, NT-proBNP and hs-CRP (c-statistic 0.75 to 0.81) (**Supplemental Tables S10-S12**).

Discussion

Our study in elderly patients with acute, haemodynamically stable PE demonstrates the strength of the PESI risk score for 6-months mortality. When adding the three cardiac biomarkers hs-cTnT, NT-proBNP and inflammatory hs-CRP to the PESI risk score, no relevant clinical benefit in risk stratification is achieved for this endpoint.

Current guidelines recommend to measure biomarkers in PE patients at intermediate risk [8]. Our data corroborate prior data on the prognostic accuracy of hs-cTnT and NT-proBNP for all-cause short-term mortality in patients with PE [8, 9]. However, from a clinical perspective our data argue in favour of using the clinical PESI risk score alone as none of the combinations of biomarkers (single or combined) with the PESI risk score provided incremental information.

In turn, the prognostic accuracy of hs-CRP in our study for all-cause mortality during 6-months follow-up was poor. Previous studies showed elevated levels of hs-CRP in patients with spontaneous VTE compared with controls [22, 23]. This association was independent of hereditary and laboratory risk factors for VTE, but lost its significance after adjustment for BMI [22, 23]. On the other hand, hs-CRP, fibrinogen, and factor VIII, were at higher levels in patients with idiopathic compared with secondary VTE controls [22, 23]. Of note, none of these studies validated the role of hs-CRP for outcome in patients with PE. Our data show that hs-CRP at the time of diagnosis does not improve risk stratification of elderly PE patients for 6-month mortality. Our study did not address whether hs-CRP obtained at a later time-point (>1 day after diagnosis of PE) is associated with adverse clinical events.

Arterial and venous thrombosis share an inflammatory pathogenesis [30]. In line with this concept, in a primary prevention setting, statin medication was found to prevent VTE in apparently healthy individuals with elevated levels of hs-CRP [31].

Hence, in contrast to atherosclerotic cardiovascular disease, the findings of the present study in patients with hemodynamically stable PE suggest that the progression of disease (as reflected by PE-related death during 6-month follow-up) may not be attributable to an inflammatory process. Further, we observed a diversity of causes of death in PE patients with

a relatively low percentage of unequivocally PE-related deaths. This observation can also be viewed in opposition to atherosclerotic cardiovascular disease, where most fatalities are clearly related to the disease itself.

In this elderly patient cohort, cancer accounted for a substantial proportion of short-term mortality (27.6%) which may act as a confounding factor for elevated hsCRP at the diagnosis of PE. Indeed, prior data demonstrated an association of hs-CRP with cancer-related mortality in cancer patients with VTE [32]. However, when we excluded patients with cancer in a subgroup analysis, we found a similarly low prognostic accuracy of hs-CRP to predict all-cause mortality as in the full cohort.

Limitations

Despite the prospective design with a large number of patients with PE enrolled receiving standardised medications and care and adjudication of adverse events by an independent committee, it was not feasible to confirm PE as cause of death by autopsy, although an association appeared clinically plausible. Yet, we do not think that this is a relevant limitation as most of the studies – particularly in elderly patients – are not able to provide this information. To account for patients with a high probability of PE as cause of death these cases were classified as “possibly PE-related”.

Furthermore, this analysis comprises a subgroup of the SWITCO65+ cohort, since biomarker data sets were not available in the entire study population. Moreover, a disparity of more than 1 day between the time of blood draw and ascertainment of data for the PESI risk score was considered inappropriate. Interestingly, the comparison between included and excluded patients in a sensitivity analysis showed that the prognostic accuracy of the PESI risk score and the biomarkers in the two groups were not markedly different. Larger studies are warranted to confirm our findings.

Given the inclusion criteria of our SWITCO-65+ cohort, this sample may not reflect the full prognostic spectrum of patients with PE because only elderly patients with age above 65 years were enrolled. Nonetheless, in our study 30% of patients had a provoked index PE,

demonstrating a low prevalence of provoked PE compared with previous studies in younger patients [30, 31].

Conclusions

The PESI risk score provides a robust discrimination of risk for death during 6 months in elderly patients with acute haemodynamically stable PE. Combining the PESI risk score with cardiac biomarkers hs-TnT, NT-proBNP and inflammatory hs-CRP did not yield a clinically relevant improvement in prognostic accuracy. Our findings indicate that hs-CRP is by far the weakest biomarker among the three analysed.

Authorship Details

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Disclosure of Conflict of Interest

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Legends to figures

Figure 1: Study Flow.

Patient enrolment and follow-up throughout the study is shown in the flow diagram.

Figure 2. Prognostic accuracy for 6-month all-cause mortality for biomarkers and PESI risk score.

Receiver operating characteristic (ROC) curve depicting the sensitivity and specificity of the pulmonary embolism severity index (PESI) risk score, high-sensitivity C-reactive protein (hs-CRP), high-sensitivity cardiac troponin T (hs-cTnT) and the precursor of brain natriuretic peptide (NT-proBNP) in the prediction of all-cause mortality during 6-month follow-up in patients with pulmonary embolism.

Legends to tables

Table 1. Clinical and laboratory characteristics.

Demographic data, comorbidities, medication and laboratory data of 214 patients with pulmonary embolism (PE) are shown. Data are shown as absolute counts (percentages) or as median (interquartile ranges). Provoked index PE: major surgery, immobilisation or oestrogen therapy during the last 3 months before index PE. VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; BMI, body mass index; AC, anticoagulation; VKA, vitamin K antagonist. Missing data exist for: BMI, n=1; Smoking status, n=2; history of major bleeding, n=1; anaemia, n=1; respiratory rate, n=38; current oestrogen therapy, n=1; D-dimer, n=13; arterial SO_2, n=15; haemoglobin, n=1; leukocytes, n=1; platelets, n=2.

Table 2. Associations of biomarkers and the PESI risk score with 6-month mortality.

Adjusted hazard ratios (HR) are adjusted for all other biomarkers and the PESI classes (ordinal), indicating an independent association with 6-month mortality. Adjusted hazard ratios are derived as stated in Methods.

Table 3. Prognostic accuracy of combinations of biomarkers with PESI risk score for 6-month mortality. Prognostic accuracy is shown by AUC, integrated discrimination improvement, and net reclassification improvement for hs-CRP and the other biomarkers added to the PESI risk score. The p-value compares the AUC of the combination against the AUC of the PESI alone. IDI: Integrated discrimination improvement for hs-CRP and the other biomarkers added to the PESI score. NRI: Net reclassification improvement for hs-CRP and the other biomarkers added to the PESI score using a probability cutoff of 15% (i.e. high risk is defined as probability of mortality >15% after 6 months which roughly corresponds to the observed mortality). The PESI score was used continuous.

Table 1. Clinical and laboratory characteristics of patients with PE

	n (%) or median (IQ-range)
Total N	N = 214
Patient age	75.0 (69.0; 82.0)
Gender (female)	90 (42%)
Prior VTE	67 (31%)
Provoked PE	64 (30%)
Active cancer	32 (15%)
Concomitant DVT	43 (20%)
BMI	27.0 (24.3; 29.9)
Smoking status	
current smoker	16 (8%)
past smoker	91 (43%)
never smoker	105 (50%)
Diabetes mellitus	30 (14%)
Coronary artery disease	38 (18%)
Chronic or acute heart failure	21 (10%)
Chronic lung disease	30 (14%)
Chronic renal disease	36 (17%)
Chronic liver disease	5 (2%)
History of major bleeding	17 (8%)
Anaemia	67 (31%)
Arterial hypertension	138 (64%)
Systolic blood pressure (mmHg)	132.5 (120.0; 150.0)
Pulse rate (per minute)	82.0 (70.8; 96.3)
Respiratory rate (per minute)	19.0 (16.0; 22.0)
Body temperature (°C)	36.6 (36.2; 37.0)
Altered mental status	6 (3%)
Current oestrogen therapy during the last 3 months	4 (2%)
Lipid-lowering drugs	63 (29%)
Statins	59 (28%)
Concomitant antiplatelet therapy	67 (31%)
Initial VKA therapy	196 (92%)
Initial parenteral anticoagulation (AC)	207 (97%)
Duration of initial AC (months)	10.0 (4.5; 25.0)
hs-CRP [mg/L]	35.5 (14.2; 84.0)
hs-cTnT [ng/L]	16.4 (8.0; 33.9)
hs-cTnT > 14 ng/L	121 (57%)
NT-proBNP [pg/mL]	646.9 (216.6; 2371.3)
NT-proBNP > 600 pg/mL	111 (52%)
D-dimer [ng/mL]	2792.0 (1556.5; 3972.0)
Arterial SO2	96.0 (92.0; 97.0)
Haemoglobin [g/dL]	13.3 (11.9; 14.4)

Leukocytes [G/L]	8.2 (6.7; 11.2)
Platelets [G/L]	203.0 (157.3; 247.8)
PESI	94.0 (80.0; 109.3)
PESI risk class	
low risk (≤85)	75 (35%)
intermediate risk (86-105)	69 (32%)
high risk (106-125)	54 (25%)
very high risk (>125)	16 (7%)

AC, anticoagulation; DVT, deep vein thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism; BMI, body mass index; VKA, vitamin K antagonist; PESI, Pulmonary embolism severity index; hs-CRP, High-sensitivity C-reactive protein; hs-cTnT, High-sensitivity cardiac Troponin T; NT-proBNP, NT-pro B-type natriuretic peptide. Provoked index PE: major surgery, immobilization, or estrogen therapy during the last 3 months before index PE. There was only one patient with very low PESI score (≤65), therefore, very low and low risk was combined.

Table 2. Associations of biomarkers and the PESI risk score with 6-month mortality

	Crude HR (95% CI)	p-value	Adjusted HR* (95%-CI)	p-value	C-statistics (95% CI)
PESI (ordinal, per risk class)#	2.28 (1.64 to 3.19)	<0.001	1.90 (1.29 to 2.79)	0.001	0.77 (0.69 to 0.84)
hs-CRP (per log-unit)	1.15 (0.91 to 1.47)	0.239	1.05 (0.80 to 1.39)	0.714	0.54 (0.44 to 0.64)
hs-cTnT (per log-unit)	1.39 (1.18 to 1.65)	<0.001	1.33 (1.10 to 1.60)	0.003	0.72 (0.62 to 0.81)
NT-proBNP (per log-unit)	1.68 (1.33 to 2.12)	<0.001	1.31 (1.04 to 1.66)	0.021	0.72 (0.63 to 0.80)

*Adjusted for all other markers and the PESI risk classes (ordinal), i.e. the association is independent of other markers/PESI.

#Models fit best if PESI classes are used ordinal rather than categorical or as continuous score (based on Akaike information criterion (AIC)).

For the rank-based C-statistics, the continuous PESI score was used.

Table 3. Prognostic accuracy of combinations of biomarkers with PESI risk score for 6-month mortality

	AUC (95% CI)	p-value*	IDI (95%-CI)	p-value	NRI (95%-CI)	p-value
PESI	0.79 (0.70 to 0.87)	-	Reference	-	Reference	-
PESI + hs-CRP	0.79 (0.70 to 0.87)	0.582	0.001 (-0.003 to 0.004)	0.596	-0.024 (-0.098 to 0.050)	0.530
PESI + hs-cTnT	0.81 (0.74 to 0.89)	0.269	0.043 (-0.004 to 0.090)	0.074	0.114 (-0.046 to 0.275)	0.163
PESI + NT-proBNP	0.80 (0.73 to 0.88)	0.554	0.041 (-0.001 to 0.084)	0.055	0.130 (-0.057 to 0.318)	0.173
PESI + all 3 biomarkers	0.82 (0.74 to 0.90)	0.391	0.067 (0.012 to 0.123)	0.018	0.101 (-0.099 to 0.302)	0.321

* The p-value compares the AUC of the combination against the AUC of the PESI risk score alone.

PESI, Pulmonary embolism severity index; hs-CRP, High-sensitivity C-reactive protein; hs-cTnT, High-sensitivity cardiac Troponin T;

NT-proBNP, NT-pro B-type natriuretic peptide; AUC, area under the ROC curve.

IDI, Integrated discrimination improvement for hs-CRP and the other biomarkers added to the PESI risk score.

NRI, Net reclassification improvement for hs-CRP and the other biomarkers added to the PESI score using a probability cutoff of 15% (i.e. high risk is defined as probability of mortality >15% after 6 months which roughly corresponds to the observed mortality).

The PESI risk score was used continuous.

FIGURES

Figure 1

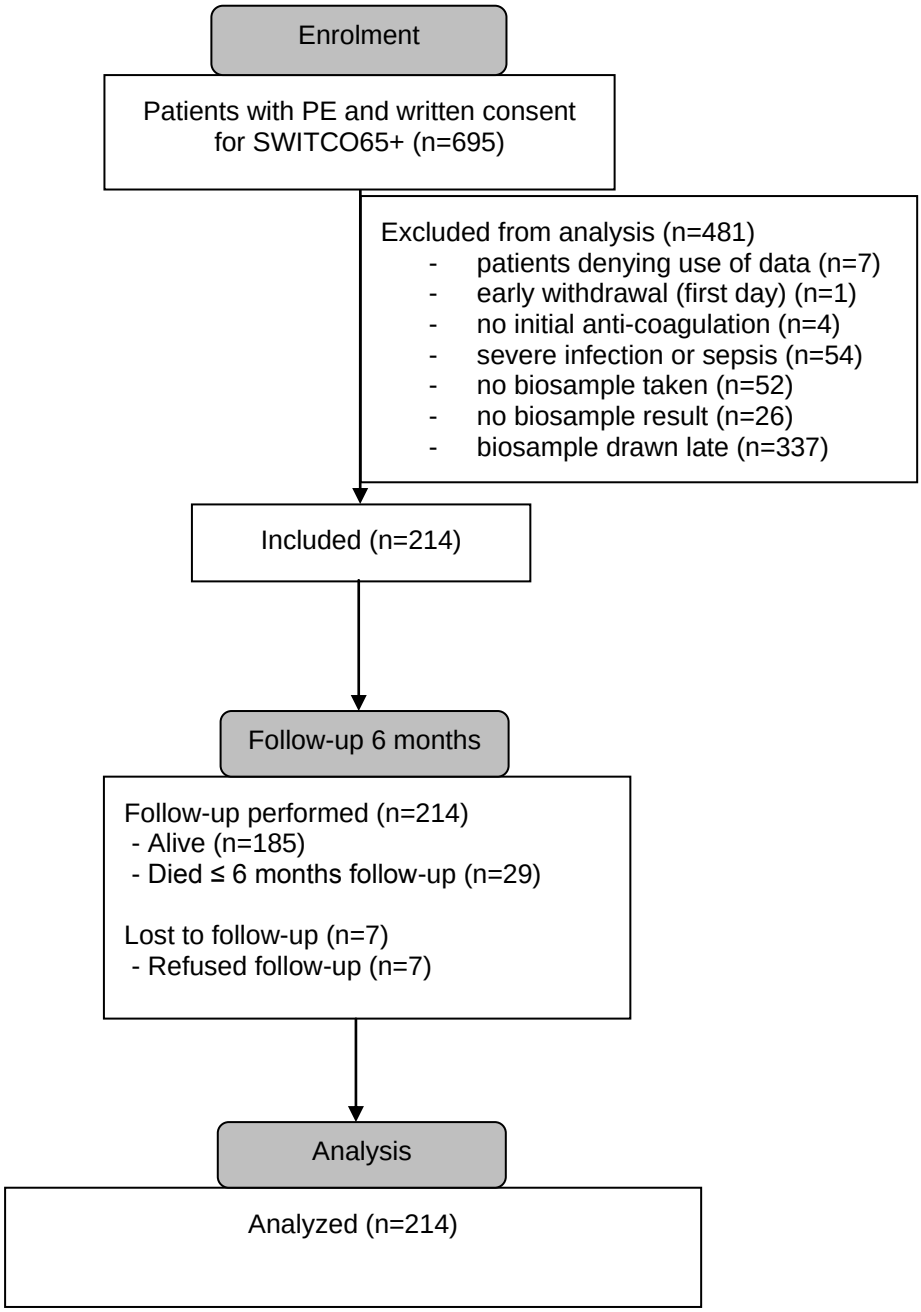

Figure 2